Day : Thursday
Date: 6/8/2006
Time: 22:45:18

PALM INTRANET

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	766	514/315.ccls.	USPAT	OR	OFF	2006/06/08 22:25
L2	9	l1 and tempol	USPAT	OR	OFF	2006/06/08 22:25
L3	567	514/330.ccls.	USPAT	OR	OFF	2006/06/08 22:42
L4	0	l3 and tempol	USPAT	OR	OFF	2006/06/08 22:25
L5	1	l3 and nitroxide	USPAT	OR	OFF	2006/06/08 22:32
L6	683	514/345.ccls.	USPAT	OR	OFF	2006/06/08 22:43
L7	571	514/376.ccls.	USPAT	OR	OFF	2006/06/08 22:43
L8	2484	l1 or l3 or l6 or l7	USPAT	OR	OFF	2006/06/08 22:43
L9	9	l8 and tempol	USPAT	OR	OFF	2006/06/08 22:43

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     (FILE 'HOME' ENTERED AT 10:17:33 ON 08 JUN 2006)

     FILE 'REGISTRY' ENTERED AT 10:17:39 ON 08 JUN 2006
L1                STRUCTURE UPLOADED
L2              0 S SSS L1 FULL
L3              0 S SSS L1 FULL
L4                STRUCTURE UPLOADED
L5            692 S SSS FULL L4

     FILE 'CAPLUS, EMBASE, BIOSIS, WPIX' ENTERED AT 10:19:41 ON 08 JUN 2006
L6           4074 S L5
L7        4263314 S TUMOR OR TUMOUR OR CANCER OR NEOPLASTIC? OR NEOPLAS? OR LEUKE
L8         118937 S P53
L9             14 S L6 AND L8
L10           283 S L6 AND L7
L11             8 DUP REM L9 (6 DUPLICATES REMOVED)
L12             8 FOCUS L11 1-
L13           206 DUP REM L10 (77 DUPLICATES REMOVED)
L14           206 FOCUS L13 1-
L15             3 S L14 AND (FRAUMENI OR ATAXIA)

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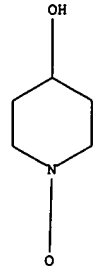

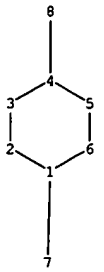

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ring nodes :
1 2 3 4 5 6
chain bonds :
1-7 4-8
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6
exact/norm bonds :
1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6

Match level :
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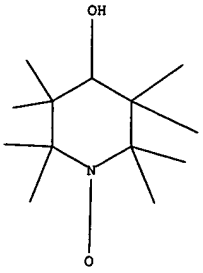
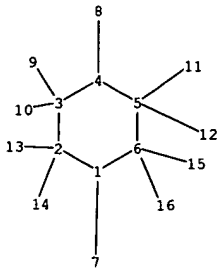
C:\Program Files\Stnexp\Queries\nitroxide.





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ring nodes :
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chain bonds :
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ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6
exact/norm bonds :
1-2 1-6 1-7 2-3 3-4 4-5 4-8 5-6
exact bonds :
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Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS

L12 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:480296 CAPLUS
DOCUMENT NUMBER: 143:166161
TITLE: Cancer chemoprevention by the antioxidant tempol acts partially via the **p53** tumor suppressor
AUTHOR(S): Erker, Laura; Schubert, Ralf; Yakushiji, Hiroyuki; Barlow, Carrolee; Larson, Denise; Mitchell, James B.; Wynshaw-Boris, Anthony
CORPORATE SOURCE: Department of Pediatrics, UCSD School of Medicine, La Jolla, CA, 92093, USA
SOURCE: Human Molecular Genetics (2005), 14(12), 1699-1708
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously demonstrated that the nitroxide antioxidant tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) increased latency to tumorigenesis and doubled (100%) the lifespan of Atm-deficient mice, a mouse model of ataxia telangiectasia, which displays accelerated oxidative damage and stress. Tempol treatment of cancer-prone **p53** -deficient mice resulted in a small but significant (25%) increase in lifespan by prolonging latency to tumorigenesis, demonstrating that existing oxidative stress and damage are not necessary for the chemopreventive effects of tempol. However, the relatively small effect on latency in **p53**-deficient mice and the finding that tempol-mediated resistance to oxidative insult was **p53**-dependent suggested a more direct role of **p53** in the chemopreventive effects of tempol. Surprisingly, tempol treatment specifically increased serine 18 phosphorylation of **p53** (but not γ-H2AX) and p21 expression in primary thymocytes in vitro in a **p53**-dependent fashion. Inhibition of phosphoinositide 3-kinase (PI3K) family members suggested that SMG-1 was responsible for the tempol-mediated enhancement of **p53** serine 18 phosphorylation. These data suggest that the chemopreventive effect of tempol is not solely due to the reduction of oxidative stress and damage but may also be related to redox-mediated signaling functions that include **p53** pathway activation.

IT Ionizing radiation
(DNA damage; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT DNA damage
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DSB reduction by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Antitumor agents
Signal transduction, biological
Transformation, neoplastic
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT **p53** (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Neoplasm
(chemoprevention; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Body weight
(not reduced by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21, induction by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Metabolic pathways
(**p53** pathway activation by tempol; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Mus musculus
(**p53**-deficient; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Phosphorylation, biological

(protein; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Oxidative stress, biological
(reduction; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT Thymus gland
(thymocyte; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT 56-45-1, Serine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(18 **p53** phosphorylation of; cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT 182970-53-2, Protein kinase Atm 402936-89-4, SMG-1 protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT **2226-96-2**, Tempol
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cancer chemoprevention by the antioxidant tempol acts partially via the **p53**)
IT 115926-52-8, Phosphoinositide 3-kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of phosphoinositide 3-kinase (PI3K) family members suggested that SMG-1 was responsible for the tempol-mediated enhancement of **p53** serine 18 phosphorylation)
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 8 EMBASE
ACCESSION NUMBER: 2005059453 EMBASE
TITLE: Role of the **p53**/p21 system in the response of human colon carcinoma cells to doxorubicin.
AUTHOR: Ravizza R.; Gariboldi M.B.; Passarelli L.; Monti E.
CORPORATE SOURCE: E. Monti, Dept. of Struct./Functional Biology, Section of Pharmacology, University of Insubria, Via A. da Giussano 10, 21052 Busto Arsizio VA, Italy.
elena.monti@uninsubria.it
SOURCE: BMC Cancer, (15 Dec 2004) Vol. 4, pp. 10p. .
Refs: 43
ISSN: 1471-2407 CODEN: BCMACL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2005
Last Updated on STN: 18 Feb 2005
AB Background: Colon adenocarcinomas are refractory to a number of widely used anticancer agents. Multifactorial mechanisms have been implicated in this intrinsically resistant phenotype, including deregulation of cell death pathways. In this regard, the **p53** protein has a well established role in the control of tumor cell response to DNA damaging agents; however, the relationship between **p53**-driven genes and drug sensitivity remains controversial. The present study investigates the role of the **p53**/p21 system in the response of human colon carcinoma cells to treatment with the cytotoxic agent doxorubicin (DOX) and the possibility to modify the therapeutic index of DOX by modulation of **p53** and/or p21 protein levels. Methods: The relationship between **p53** and p21 protein levels and the cytotoxic effect of DOX was investigated, by MTT assay and western blot analysis, in HCT116 (**p53**-positive) and HT29 (**p53**-negative) colon cancer

cells. We then assessed the effects of DOX in two isogenic cell lines derived from HCT116 by abrogating the expression and/or function of **p53** and p21 (HCT116-E6 and HCT116 p21-/-, respectively). Finally, we evaluated the effect of pre-treatment with the piperidine nitroxide Tempol (TPL), an agent that was reported to induce p21 expression irrespective of **p53** status, on the cytotoxicity of DOX in the four cell lines. Comparisons of IC50 values and apoptotic cell percentages were performed by ANOVA and Bonferroni's test for independent samples. C.I. calculations were performed by the combination Index method. Results: Our results indicate that, in the colon carcinoma cell lines tested, sensitivity to DOX is associated with p21 upregulation upon drug exposure, and DOX cytotoxicity is potentiated by pretreatment with TPL, but only in those cell lines in which p21 can be upregulated. Conclusions: p21 induction may significantly contribute to the response of colon adenocarcinomas cells to DOX treatment; and small molecules that can exploit **p53**-independent pathways for p21 induction, such as TPL, may find a place in chemotherapeutic protocols for the clinical management of colorectal cancer, where **p53** function is often lost, due to genetic or epigenetic defects or to post-transcriptional inactivating mechanisms.

L12 ANSWER 3 OF 8 CAPLUS
ACCESSION NUMBER: 2004:831323 CAPLUS
DOCUMENT NUMBER: 142:34547
TITLE: The effects of antioxidants on radiation-induced apoptosis pathways in TK6 cells
AUTHOR(S): Samuni, Ayelet M.; DeGraff, William; Cook, John A.; Krishna, Murali C.; Russo, Angelo; Mitchell, James B.
CORPORATE SOURCE: Radiation Biology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Free Radical Biology & Medicine (2004), 37(10), 1648-1655
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study was designed to determine if radiation-mediated activation of the apoptotic pathways would be influenced by antioxidants and if a correlation would be found between radioprotection and changes in transduction pathways. Human lymphoblastoid TK6 cells, known to undergo apoptosis as a result of radiation, were irradiated (6 Gy) with and without antioxidants, and then whole-cell lysates were collected. Parallel studies were conducted to assess the survival (clonogenic assay) and apoptotic index. The impacts of two nitroxide antioxidants, tempol and CAT-1, differing in cell permeability, as well as the sulfhydryl antioxidant N-acetyl-L-cysteine (L-NAC), were estimated Changes in apoptotic pathway proteins and **p53** were assessed by Western blotting. Fraction of apoptotic cells was determined by flow cytometry. Tempol (10 mM), which readily enters cells, partially radioprotected TK6 cells against clonogenic killing, but had no effect on radiation-induced apoptotic parameters such as cleaved caspase 3 or cleaved PARP. Tempol alone did not induce cytotoxicity, yet did increase cleaved PARP levels. The radiation-induced increase in **p53** protein was partly inhibited by tempol, but was unaffected by CAT-1 and L-NAC. Both CAT-1 (10 mM), which does not enter cells, and L-NAC (10 mM) had no radioprotective effect on cell survival. Although L-NAC did not protect against radiation-induced cytotoxicity, it completely inhibited radiation-induced increase in cleaved caspase 3 and cleaved PARP. Collectively, the results question the validity of using selected apoptosis pathway members as sole indicators of cytotoxicity.
IT Antioxidants
Apoptosis
Human
Ionizing radiation
Lymphoblast
Radioprotectants
Transduction, genetic
(antioxidants effect on radiation-induced apoptosis)

IT **p53** (protein)
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidants effect on radiation-induced apoptosis)
IT 9055-67-8, Poly(ADP-ribose) polymerase 169592-56-7, Caspase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antioxidants effect on radiation-induced apoptosis)
IT 616-91-1, N-Acetyl-L-cysteine **2226-96-2**, Tempol 64486-64-2, CAT-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidants effect on radiation-induced apoptosis)
REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:720111 CAPLUS
DOCUMENT NUMBER: 134:36766
TITLE: The nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells
AUTHOR(S): Gariboldi, M. B.; Rimoldi, V.; Supino, R.; Favini, E.; Monti, E.
CORPORATE SOURCE: Section of Pharmacology, Department of Structural and Functional Biology, University of Insubria, Varese, Milan, Italy
SOURCE: Free Radical Biology & Medicine (2000), 29(7), 633-641
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antiproliferative effect of Tempol, a stable nitroxide free radical, was investigated on the **p53**-neg. human leukemia cell line HL60. A concentration- and time-dependent inhibition of cell growth was observed that appears to be due to induction of apoptosis. Involvement of oxidative stress is indicated by a concentration-dependent increase in intracellular peroxides and a parallel decrease in total cellular glutathione; in addition, increased survival rates were observed in cells simultaneously treated with Tempol and the antioxidant N-acetylcysteine. Tempol did not affect the relative levels of Bax and Bcl2, whereas p21WAF1/CIP1 was enhanced in a concentration- and time-dependent fashion; this effect was partially inhibited by N-acetylcysteine, was maintained for up to 8 h after Tempol removal, and seemed to depend on continuing protein synthesis. The increase in p21WAF1/CIP1 was accompanied by a parallel accumulation of cells in the G1 phase of the cycle and by a decrease in the 110 kDa form of pRb. Our results suggest that **p53**-independent induction of p21WAF1/CIP1 mediates the antiproliferative effect of Tempol; on the basis of this observation, the nitroxide could be proposed as an useful adjunct to the treatment of **p53**-deficient tumors, which are often refractory to standard chemotherapy.
IT Interphase (cell cycle)
(G1-phase; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)
IT Animal cell line
(HL-60; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)
IT Transcription factors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Rb, 110,00-mol.-weight; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, decreased pRb levels and cell death in HL60 cells)
IT Antitumor agents
(leukemia; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)
IT Peroxides, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(lipid; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)
IT Apoptosis

Oxidative stress, biological
Proliferation inhibition
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT Translation, genetic
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells dependent on)

IT Cyclin dependent kinase inhibitors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(p21CIP1/WAF1; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT Lipids, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(peroxides; nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT 70-18-8, Glutathione, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

IT **2226-96-2**, Tempol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitroxide Tempol induces oxidative stress, p21WAF1/CIP1, and cell death in HL60 cells)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:14804 CAPLUS
DOCUMENT NUMBER: 142:254009
TITLE: The piperidine nitroxide Tempol potentiates the cytotoxic effects of temozolomide in human glioblastoma cells
AUTHOR(S): Ravizza, Raffaella; Cereda, Elena; Monti, Elena; Gariboldi, Marzia B.
CORPORATE SOURCE: Department of Structural and Functional Biology, Section of Pharmacology, University of Insubria, Busto Arsizio, I-21052, Italy
SOURCE: International Journal of Oncology (2004), 25(6), 1817-1822
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Temozolomide (TMZ) is a methylating agent with promising antitumor efficacy for the treatment of melanomas and intermediate-grade gliomas. Unfortunately, its use in the management of high-grade gliomas (glioblastomas) is limited by multifaceted resistance mechanisms. The aim of this study was to evaluate the possibility to improve the cytotoxic response of two human glioblastoma cell lines, U87MG and U373MG, to TMZ by the use of Tempol (TPL), a low mol. weight piperidine nitroxide that has been shown to inhibit in vitro and in vivo growth of murine glioma cells. To this purpose, we used two different schedules for the combined exposure to the two agents. Our data indicate that TPL synergizes with TMZ in both U87MG and U373MG cells for both schedules tested. This effect is accompanied by an increase in apoptotic cell death and by changes in the expression of genes involved in control of the apoptotic process. TPL was also observed to induce a cell-type specific decrease in GSH levels and in GSH-related enzyme activities that could contribute to its sensitizing effect.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bax; exposure to TMZ had no effect on Bax level in human glioblastoma cell lines U87MG and U373MG whereas TPL caused dose-dependent increase in protein level in U373MG cell line while no effect was seen in U87MG cell line)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-2; Bcl-2 level was unchanged following exposure to temozolomide and tempol in human glioblastoma cell lines U87MG and U373MG)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-xL; exposure to TPL had no effect on Bcl-XL level in human glioblastoma cell lines U87MG and U373MG whereas TMZ caused dose-dependent increase in protein level in U87MG cell line while no effect was seen in U373MG cell line)

IT Methylation
(agents; methylating agent temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT Antitumor agents
(anticancer agent temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT Neuroglia, neoplasm
(glioblastoma; temozolomide cytotoxicity increased dose-dependently by tempol treatment, increased apoptosis was seen in human glioblastoma cell lines U87MG and U373MG)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21; exposure to tempol and high dose TMZ caused dose-dependent increase in p21 level in human glioblastoma cell line U373MG while no effect was seen in U87MG cell line)

IT **p53** (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**p53** level was unchanged following exposure to temozolomide and tempol in human glioblastoma cell lines U87MG and U373MG)

IT Drug interactions
(synergistic; temozolomide cytotoxicity increased dose-dependently by tempol treatment exhibiting synergistic effect in human glioblastoma cell lines U87MG and U373MG)

IT Human
(temozolomide cytotoxicity increased dose-dependently by tempol treatment, increased apoptosis was seen in human glioblastoma cell lines U87MG and U373MG)

IT Apoptosis
(temozolomide treatment in combination with tempol induced dose-dependent increase in apoptosis more than monotherapy in human glioblastoma cell lines U87MG and U373MG)

IT 70-18-8, Glutathione, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exposure to tempol caused significant decrease in GSH level in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 9001-48-3, Glutathione reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exposure to tempol caused significant decrease in GSR level in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 50812-37-8, Glutathione transferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exposure to tempol caused significant decrease in GST activity in U373MG human glioblastoma cell line while no effect was seen in U87MG cell line)

IT 85622-93-1, Temozolomide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(temozolomide cytotoxicity increased dose-dependently by tempol treatment in human glioblastoma cell lines U87MG and U373MG)

IT **2226-96-2**, Tempol
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tempol treatment increased cytotoxicity of temozolomide dose-dependently in human glioblastoma cell lines U87MG and U373MG)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 8 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003115021 EMBASE
TITLE: Study of in vitro and in vivo effects of the piperidine nitroxide Tempol - A potential new therapeutic agent for gliomas.
AUTHOR: Gariboldi M.B.; Ravizza R.; Petterino C.; Castagnaro M.; Finocchiaro G.; Monti E.
CORPORATE SOURCE: E. Monti, DBSF, Laboratory of Pharmacology, University of Insubria, Via A. da Giussano, 12, 21052 Busto Arsizio (VA), Italy. elena.monti@uninsubria.it
SOURCE: European Journal of Cancer, (2003) Vol. 39, No. 6, pp. 829-837. .
Refs: 28
ISSN: 0959-8049 CODEN: EJCAEL
PUBLISHER IDENT.: S 0959-8049(02)00742-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Mar 2003
Last Updated on STN: 27 Mar 2003

AB The identification of novel therapeutic agents for the management of malignant gliomas represents an area of active research. Here, we show that Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl; TPL), a stable nitroxide free radical, inhibits the growth of C6 glioma cells both in vitro and in vivo. Morphological features of apoptosis were apparent in C6 cells following in vitro treatment with TPL. Cell death was preceded by dose-dependent increase in p21(WAF1/CIP1) expression, without apparent stabilisation of the TP53 gene product. When C6 cells were grown as xenografts in nude mice, treatment with TPL induced a significant dose-dependent decrease in tumour growth, without signs of general or organ toxicity. Tumours from treated mice showed an increase in the number of apoptotic cells and a decrease in the rate of neo-vascularisation compared with tumours from control mice. Our findings suggest a potential use for TPL as a novel antiproliferative agent for the treatment of malignant gliomas. .COPYRGT. 2003 Elsevier Science Ltd. All rights reserved.

L12 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:441858 BIOSIS
DOCUMENT NUMBER: PREV200300441858
TITLE: Effects of p21waf1/cip1 expression in the response of human colon cancer cells to doxorubicin.
AUTHOR(S): Monti, Elena [Reprint Author]; Ravizza, Raffaella [Reprint Author]; Cereda, Elena [Reprint Author]; Gariboldi, Marzia B. [Reprint Author]
CORPORATE SOURCE: DBSF, University of Insubria, Busto Arsizio, VA, Italy
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 132. print.
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ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
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IT Major Concepts
Digestive System (Ingestion and Assimilation); Pharmacology; Tumor Biology
IT Diseases
colon cancer: digestive system disease, neoplastic disease
Colonic Neoplasms (MeSH)

IT Chemicals & Biochemicals
doxorubicin: antineoplastic-drug, efficacy; p21: expression;
p21-waf1/cip1: expression; **p53**: expression; tempol
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HCT116 cell line (cell line): human colon cancer cells
HT29 cell line (cell line): human colon cancer cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 23214-92-8 (doxorubicin)
2226-96-2 (tempol)

L12 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:369567 BIOSIS
DOCUMENT NUMBER: PREV200100369567
TITLE: Synergistic antiproliferative effects of the piperidine nitroxide Tempol and Temozolomide against human glioma cell lines.
AUTHOR(S): Gariboldi, Marzia B. [Reprint author]; Ravizza, Raffaella [Reprint author]; Rimoldi, Valeria [Reprint author]; Monti, Elena [Reprint author]
CORPORATE SOURCE: University of Insubria, Milan, Italy
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 84-85. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002
IT Major Concepts
Pharmacology; Tumor Biology
IT Diseases
malignant glioma: neoplastic disease
Glioma (MeSH)
IT Chemicals & Biochemicals
GSH [glutathione]; Temezolamide: antineoplastic-drug, piperidine nitroxide, synergistic effects; Tempol: antineoplastic-drug, piperidine nitroxide, synergistic effects; cip1; **p53**; waf1
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
U373 cell line: human glioma cells
U87 cell line: human glioma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
C6 cell line: mouse glioma cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 70-18-8 (GSH)
70-18-8 (glutathione)
2226-96-2 (Tempol)

Atlas of Genetics and Cytogenetics in Oncology and Haematology

Ataxia telangiectasia

Identity

Note	see also, in Deep Insight section: **Ataxia**-Telangiectasia and variants
Other names	Louis-Bar syndrome
Inheritance	autosomal recessive; frequency is about 1 to 2.5/105 newborns; heterozygotes are estimated to be 1% of the general population; founder effect are found in some isolated population

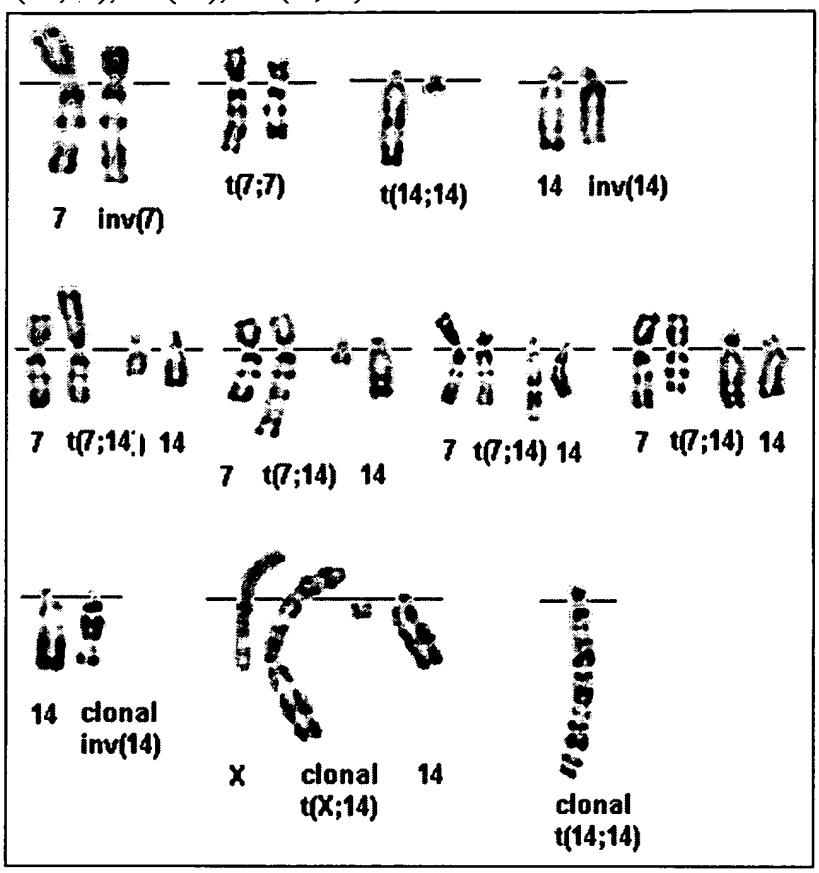
Clinics

Note	**ataxia** telangiectasia is a chromosome instability syndrome with cerebellar degeneration, immunodeficiency, and an increased risk of cancers; A-T cells are defective in recognizing double-strand DNA damage to signal for repair
Phenotype and clinics	• onset of the disease is often noted during the second year of life: there is progressive cerebellar **ataxia** (initially truncal, with further peripheral extension); **ataxia** is a constant feature in this disease; oculomotor apraxia, dysarthria, and dystonia; leading to muscular atrophia • telangiectasia: facial region exposed to sunlight, and eyes (conjunctiva) • combined immunodeficiency (in 70 %): thymus hypoplasia, and IgG2 and 4, IgA, IgE deficiency • other features: growth retardation; hypogonadism; occasionally diabetes mellitus
Neoplastic risk	• risk of cancers is X 100, consisting mainly of T- cell malignancies (a 70-fold and 250-fold increased risks of leukemia and lymphoma respectively) and B-cell malignancies, but not myeloid leukemia; carcinomas of the skin, ovary, breast, and stomach have also been described • cancer treatment is complicated by radiation- and chemo-sensitivity
Evolution	progressive cerebellar degeneration: patients are usually in a wheelchair by the age of ten
Prognosis	• respiratory infection is the common cause of death, with cancer being the second most common. • survival is often into fourth decade today where optimal medical care is available

Cytogenetics

Inborn conditions

- spontaneous chromatid/chromosome breaks, triradials, quadriradials (less prominent phenomenon than in Fanconi anaemia); telomeric associations
- the best diagnosis test is on the (pathognomonic) highly elevated level (10% of mitoses) of inv(7)(p14q35), t(14;14)(q11;q32), and other non clonal stable chromosome rearrangements involving 2p12, 7p14, 7q 35, 14q11, 14q32, and 22q11 (illegitimate recombinations between immunoglobulin superfamilly genes Ig and TCR); normal level of those rearrangements are: 1/500 (inv(14)), 1/200 (t(7;14)), 1/10 000 (inv(7))
- clonal rearrangements further occur in 10% of patients, but without manifestation of malignancy: t(14;14), inv(14), or t(X;14)



Sporadic (rows 1 and 2) and clonal (row 3) rearrangements in **ataxia** telangiectasia (R- banding). Row 1, from left to right: inv(7)(p14q35), t(7;7)(p14;q35), t(14;14)(q11;q32), inv(14)(q11q32); Row 2:, from left to right: t(7;14)(p14;q11), t(7;14)(q35;q11), t(7;14)(p14;q32), t(7;14)(q35;q32); Row 3, from left to right: inv(14)(q11;q32), t(X;14)(q28;q11) (note the late replicating X on the left), t(14;14)(q11;q32) - Courtesy Alain Aurias (modified figure reprinted from Médecine/Sciences 1986; 2: 298-303., by permission of the publisher Masson).

Cytogenetics of cancer

clonal rearrangements in T-cell ALL and T-PLL (prolymphocytic leukaemia) in AT patients are complex, with the frequent involvement of t(14;14)(q11;q32)(q11;q32), or t(X;14)(q28;q11), implicating the genes TCL1 or MTCP1 respectively, as is found in T-PLL in non-AT patients

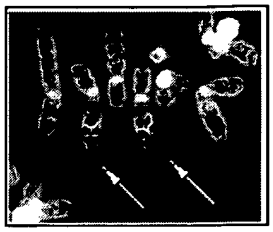
Other findings

Note

- high sensitivity to ionizing radiations and to radiomimetic drugs (diagnostic may in part be based on the hypersensitivity of AT lymphocytes to killing by gamma irradiation); cell irradiation does not inhibit S phase (DNA synthesis): this is quite pathognomonic of AT, and shows that G1 checkpoint is deficient; there is a lack of **P53**, GADD45 and P21 induction, and a fall in radiation-induced apoptosis; **P53** phosphorylation at ser15 is deficient
- lenthening of the cell cycle
- difficult to grow cells with phytohemaglutinin: karyotypes should be performed with interleukine 2 in 4 days cultures
- other: increased level of serum alpha-fetoprotein

Genes involved and Proteins

Gene Name ATM (**Ataxia** telangiectasia mutated) is responsible for the vast majority of A -T cases.
Location 11q22-q23.1
DNA/RNA



ATM (11q22.3) in normal cells: PAC 891P24 - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are wellcome: contact M Rocchi

Description 66 exons spanning 184 kb of genomic DNA

Protein

Description 3056 amino acids; 350 kDa; contains a Pl 3-kinase-like domain
Localisation mostly in the nucleus in replicating cells, cytoplasm in differentiating cells
Function mediates cell cycle arrest in response to ionizing radiation through the phophorylation of targets including **p53**, cAbl, BRCA1, H2AX, IkB-alpha and chk1

Mutations

Germinal various types of mutations, dispersed throughout the gene, and therefore most patients are compound heterozygotes; however, most mutations appear to inactivate the **ATM** protein by truncation, large deletions, or annulation of initiation or termination. Missense mutations have been described in breast cancer patients, but do not seem to contribute to **ataxia**-telangiectasia.

To be noted

- heterozygote cancer risk: the relative risk of breast cancer in A-T heterozygote women has been estimated through epidemiological studies to be 3.9 (CI 2.1-7.1), and through haplotype analysis to be 3.32 (CI 1.75-6.38); since the A-T heterozygote frequency is about 1 %, 2-4 % of breast cancer cases may be due to **ATM** heterozygosity; the risk of other types of cancer in A-T heterozygotes is low
- the A-T variant Nijmegen breakage syndrome does not involve the same gene.

External links

GeneCards	**ATM**
GDB	**ATM**
OMIM	208900
Orphanet	**Ataxia** telangiectasia
HGMD	593364
Other database	**Ataxia**-Telangiectasia - GeneClinics
Association	The A-T Children's Project

Association	**Ataxia**-Telangiectasia Mutation Database
Registry	http://www.vmmc.org/vmrc/**atm**.htm

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Medline 11571274

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Contributor(s)

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Updated	10-1999	Nancy Uhrhammer, Jacques-Olivier Bay and Richard A Gatti
Updated	10-2002	Nancy Uhrhammer, Jacques-Olivier Bay and Richard A Gatti

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Huret JL . **Ataxia** telangiectasia. Atlas Genet Cytogenet Oncol Haematol. April 1998 .
URL : http://www.infobiogen.fr/services/chromcancer/Kprones/**ataxia**.html

Uhrhammer N, Bay JO, Gatti RA . **Ataxia** telangiectasia. Atlas Genet Cytogenet Oncol Haematol. October 1999 .
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URL : http://www.infobiogen.fr/services/chromcancer/Kprones/**ataxia**.html

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For comments and suggestions or **contributions**, please contact us
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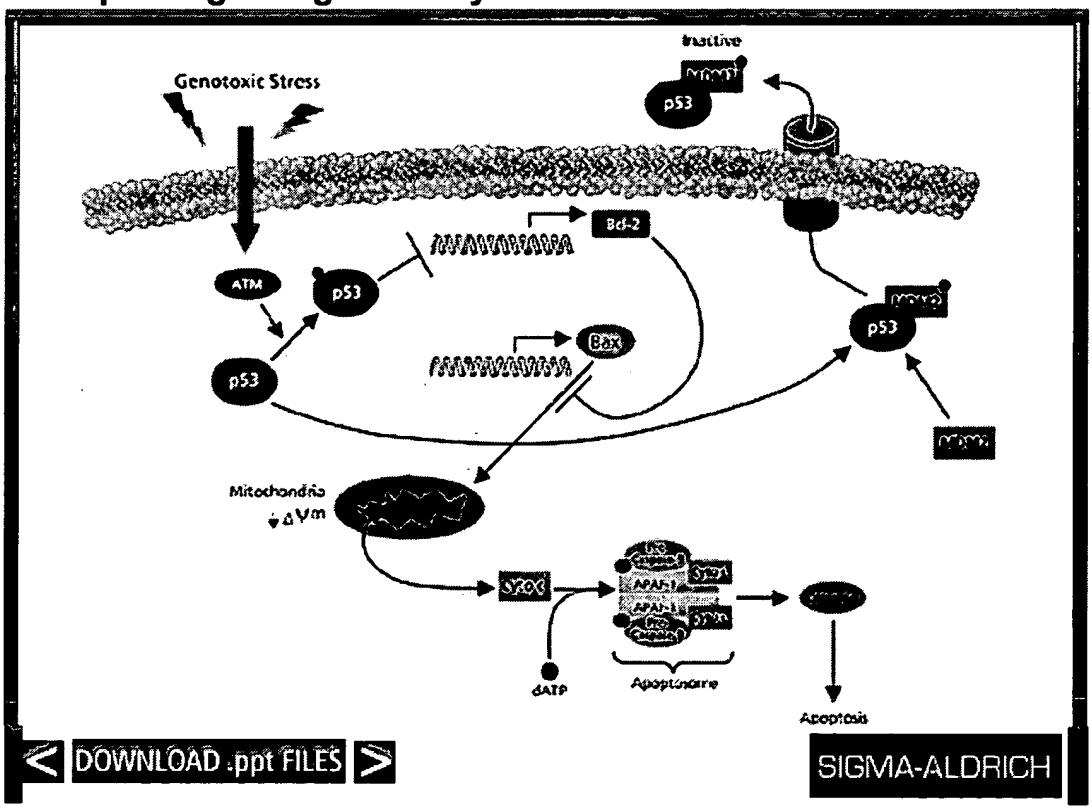
ATM/p53 Signaling Pathway



Slides

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ATM/p53 Signaling Pathway

The **ataxia** telangiectasia-mutated gene (**ATM**) encodes a protein kinase that acts as a tumor suppressor. **ATM** activation, via IR damage to DNA, stimulates DNA repair and blocks cell cycle progression. One mechanism through which this occurs is **ATM** dependent phosphorylation of **p53**. **p53** can cause growth arrest of the cell at a checkpoint to allow for DNA damage repair or can cause the cell to undergo apoptosis if the damage

cannot be repaired. The critical role of **p53** is evident by the fact that it is mutated in over 50% of all human cancers.

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1: Cell. 1996 Jul 12;86(1):159-71.

Cell Press

Atm-deficient mice: a paradigm of ataxia telangiectasia.

Barlow C, Hirotsune S, Paylor R, Liyanage M, Eckhaus M, Collins F, Shiloh Y, Crawley JN, Ried T, Tagle D, Wynshaw-Boris A.

Laboratory of Genetic Disease Research, National Center for Human Genome Research, National Institutes of Health, Bethesda, Maryland 20892, USA.

A murine model of ataxia telangiectasia was created by disrupting the Atm locus via gene targeting. Mice homozygous for the disrupted Atm allele displayed growth retardation, neurologic dysfunction, male and female infertility secondary to the absence of mature gametes, defects in T lymphocyte maturation, and extreme sensitivity to gamma-irradiation. The majority of animals developed malignant thymic lymphomas between 2 and 4 months of age. Several chromosomal anomalies were detected in one of these tumors. Fibroblasts from these mice grew slowly and exhibited abnormal radiation-induced G1 checkpoint function. Atm-disrupted mice recapitulate the ataxia telangiectasia phenotype in humans, providing a mammalian model in which to study the pathophysiology of this pleiotropic disorder.

MeSH Terms:

- Animals
- Ataxia Telangiectasia/genetics
- Ataxia Telangiectasia/immunology
- Ataxia Telangiectasia/physiopathology*
- Cell Cycle/genetics
- Cell Cycle Proteins
- Cell Division/genetics
- DNA-Binding Proteins
- Disease Models, Animal
- Dose-Response Relationship, Radiation
- Female
- Fibroblasts/cytology
- Fibroblasts/physiology
- Germ Cells/cytology
- Germ Cells/physiology
- Leucine Zippers/genetics
- Lymphoma/genetics
- Male
- Mice

- Mice, Mutant Strains
- Mutation/immunology
- Mutation/physiology
- Mutation/radiation effects
- Neurologic Examination
- Protein-Serine-Threonine Kinases*
- Proteins/genetics*
- Research Support, U.S. Gov't, P.H.S.
- Thymus Neoplasms/genetics
- Tumor Suppressor Proteins

Substances:

- Cell Cycle Proteins
- DNA-Binding Proteins
- Proteins
- Tumor Suppressor Proteins
- Protein-Serine-Threonine Kinases
- ataxia telangiectasia mutated protein

PMID: 8689683 [PubMed - indexed for MEDLINE]
